REMARKS

Claims 1-48 are now pending for prosecution in this case. Claims 19-48 have been withdrawn from considerations as being drawn to a non-elected invention. Claims 1-18 have been rejected/objected to on various grounds, which have been traversed in the appropriate sections below. As submitted herewith, Claims 1-13 and 15 are amended.

Objections/Comments

Priority

The Examiner has indicated that the Applicants elected invention, specifically, SEQ ID NO:1, SEQ ID NO:4 and ATCC Dep. No. PTA-3376 (DNA 146649-1789R1) is not supported by the disclosure of Provisional Application No. 60/212,901, filed 20 June 2000.

In response, Applicants do not contest the Examiner's priority finding.

Drawings

The Examiner has objected to the drawings under 37 C.F.R. § 1.84(p)(5) allegedly because reference characters mentioned in the drawings are not mentioned in the specification. Specifically, the Examiner indicates that while Example 11 is directed to transgenic mice, it fails to mention any reference to the "transgenic mice figures" or Figures 3A-3C.

In response, Applicants respectfully submit that while Example 11 is a prophetic example describing how the polypeptides of the invention can be tested in a mouse model, the "Brief Description of the Drawings" at page 11, lines 6-8 indeed refers to and describes Figures 3A-3C.

Claim Objections

Claims 1-9, 11 and 15 are objectionable because they contain subject matter drawn to non-elected inventions.

In response, and especially in light of the holding of different priorities for the described species sequences, Applicants have redrafted the subject claims to be directed to the elected invention.

However, Applicants reiterate their argument that exclusion of this subject matter is *not* proper restriction practice. The Examiner indicates that each sequence is patentably distinct because it is "composed of unrelated or diverse sequences, different coding regions and . . . structural and functional differences." While Applicants do not contest the Examiner's holding of patentable distinctiveness between these three species sequences, the similarities between the primary structure of the amino acid sequences shown in Figure 4 (and repeated below) does not support this stated rational for restriction. Applicants reiterate their prior argument that under M.P.E.P § 809.02(c)(B)(1), the proper procedural manner for handling this would have been to require election of a single species, and then when examination found that species free of the prior art, to then search the remaining species.

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DNA146649     1 MAILTLSLQLILLLIPSISHEAHKTSLSSWKHDQDWANVSNMTFSNGKLR
DNA149986     1 MAILMLSLQLILLLIPSISHEAHKTSLSSWKHDQDWANVSNMTFSNGKLR
DNA149995     1 MAILTLSLQLILLLIPSISHEAHKTSLSSWKHDQDWANVSNMTFSNGKLR

DNA146649    51 VKGIYYRNADICSRHRVTSAGLTLQDLQLWCNLRIIH--------
DNA149986    51 VKGIYYRNADICSRHRVTSAGLTLQDLQLWCNLRSVARGQIPSTL
DNA149995    51 VKGIYYRNADICSRHRVTSAGLTLQDLQLWCNLRSVARGQIPSTL
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The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 6-12 and 18 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Specifically, the Examiner has alleged that the following claims are indefinite for various reasons. because: (1) claims 6 and 7 because of the language "full-length polypeptide coding sequence"; (2) claim 9 because it is not clear what is intended; (3) claims 8, 10 and 11 because stringency is relative and there is no unambiguous definition for this term; (4) claim 12 because it refers back to claim 12 and (5) claim 18 because it ultimately depends from claim 1, which recites a complement, and a complement cannot produce a polypeptide.

In response, claims 6 and 7 have been amended to eliminate the observed ambiguity. Claim 9 has been amended to clarify the probe strand of the hybridization reaction. Claim 8 has been amended to clarify hybridization under at least moderately stringent condition, as defined at page 17, lines 14-19, while Claim 10 has been amended to clarify the stringent conditions defined at page 17, lines 3-11. Claim 12 has been amended to correct the dependency from Claim 11. Claim 13 has been amended to more precisely refer to the coding sequence of Claim 1, and in so doing, corrected the alleged ambiguity of dependent claims 13, 14, 16-18.

A typographical error present in the description of the moderately stringent conditions present in the original text at page 17, line 17 has also been corrected. This error stated that the concentration of background salmon sperm DNA was 20 mg/ml, rather than 20 μg/ml. The correction is not new matter. The specification defines stringency as the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. It is plainly clear to one of ordinary skill that moderately stringent conditions means reaction conditions where annealing can take place more easily, and that the levels of background DNA, which might interfere with the desired DNA strand from annealing to its target, should be lower, not higher.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6-12 and 18 under 35 U.S.C. § 112. Second Paragraph.

The Rejection under 35 U.S.C. § 101

Claims 1-18 stand rejected under 35 U.S.C. § 101, because the claimed invention allegedly is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Specifically, the Examiner asserts that the disclosed data is insufficient to support a utility because it is not allegedly clear how the DNA or encoded protein affects a body weight disorder or is involved in the control of body weight. More particularly, the Examiner notes the following: (1) there is no indication in Example 11 which NS4 cDNA was employed to make transgenic mice; (2) there is no reference to any figure that supports the data; (3) it isn't clear whether the standard lab chow fed to the mice was high fat or low fat; (4) the specification fails to disclose the length of time the transgenic and control mice were fed prior to the recording of

the measurements and (5) it isn't clear if the invention affects endpoint body mass or growth rate.

In response, Applicants agree that while Example 11 is a prophetic example describing how the polypeptides of the invention can be tested in a transgenic animal model, the data and the particular NS4 gene used to make the transgenic animal is reported in the description of Figures 3A-3C at page 11, lines 6-8. Regardless of what type of food was fed to the mice, how long they were fed it, or whether growth rate or final body mass is affected, the critical conclusion is the relative effect that transgenic mice that express NS4 v. control mice who do not. The data points reported in Figure 3A-3C clearly indicate that transgenic NS4 expression results in (1) lower total weight, (2) lower fat/total body weight ratio and (3) greater lean muscle mass/total body weight ratio.

The reduction in body weight in combination with increased lean muscle mass is a specific and substantial utility. This utility is specific because this observed effect is seen in transgenic animals expressing DNA146649-1789R1 (SEQ ID NO:1).

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-18 under 35 U.S.C. § 101.

The First Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-18 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because as the claimed invention is not supported by either a credible, specific and substantial utility, as asserted above, one skilled in the art clearly would not know how to use the claimed invention.

In response, Applicants traversal of the rejection of claims 1-18 as lacking a credible, specific and substantial utility is dispositive of this rejection as well.

The Second Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 11-14, 16-18 stand rejected under 35 U.S.C.§ 112, first paragraph, allegedly because the specification does not enable variants or fragments of an NS4 polypeptide. Specifically, the Examiner has alleged that the specification does not teach how to make NS4 variants or does it provide an assay to evaluate the function of any modified polypeptide. Moreover, the Examiner continues, the specification does not support claims to variant NS4

polynucleotides modified to an unlimited extent. As a result, the Examiner concludes, that in order for a reasonable assurance that such variant has desirable properties of the invention, identification of the particular regions responsible for the biological function, and those which are tolerant to mutations is necessary.

The Examine then applies the *Wands* factors as support for her rejection, including (1) the large quantity of experimentation necessary to generate the infinite number of derivatives, (2) the lack of direction/guidance presented in the specification regarding which structural features are required for activity, (3) the absence of working examples, (4) the complex nature of the invention, (5) the state of the prior art which established the unpredictability of the effects of mutation on protein structure and function, (6) the breadth of the claims which fail to recite any structural or functional limitation, in support of her finding of the use of undue experimentation by the skilled artisan to make and/or use the claimed invention in its full scope.

In response, Applicants respectfully disagree that the specification does not teach how to make NS4 variants, or to evaluate their function. The preparation of NS4 variants is described at page 40, line 19 through page 44, line 21. The preparation of NS4 polypeptides, including native sequence and variants thereof is described at page 44, line 23 through page 50, line 18. The "functional assay" to determine NS4 biological activity is the transgenic animal model described in Example 11. Next, Applicants claim scope is not unlimited, as suggested by the Examiner. Moreover, the claim scope, as now defined, comprehends nucleic acid molecules that encode polypeptides bearing 80% sequence identity to SEQ ID NO:4.

The Examiner has further cited Wells, *Biochemistry* 29:8509-8517 (1990), for the proposition that polypeptide function is extremely sensitive to changes in the primary structure. Applicants hereby provide Bowie *et al.*, *Science* 247: 1306-1310 (1990), in support of their argument to the Examiner that polypeptide function is indeed largely tolerant to residue primary structure residue substitutions.

Next, Applicants respectfully submit that enablement requirement of 35 U.S.C. § 112, First Paragraph requires that the specification describe to one of ordinary skill how to (a) *make* and (b) *use* the invention, without *undue* experimentation. As articulated by the Federal Circuit:

[E]nablement is not precluded by the necessity for some experimentation such as routine screening. However, [the] experimentation needed to practice the invention must not be undue . . . "the key word is 'undue,' not experimentation."

In re Wands, 8 U.S.P.Q.2d. 1400, 1404 (Fed. Cir. 1988)

Wands also provides guidance in determining enablement. These "Wands factors", as they have become known, are the following: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Wands* at 1404. Moreover, a specification is entitled to a presumption of enablement, unless there is reason to doubt the objective truth of the statements contained therein. *In re Marzocchi & Horton*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

In *Wands*, the Federal Circuit reversed a decision of the Board of Patent Appeals and Interferences that affirmed an Examiner's rejection for want of enablement. The claimed subject matter was an immunoassay method to detect hepatitis B surface antigen using high-affinity monoclonal IgM antibodies. At issue was whether the ability to make monoclonal antibodies from readily available starting materials, using well known methods, enabled the production of the particular high affinity IgM antibodies of the invention.

In applying the above "*Wands* factors," the Federal Circuit reviewed the methodology of the production of monoclonal antibodies beginning with animal immunization, spleen removing, fusion with myeloma cells, screening and selection of the resulting hybridomas, cloning the desired antibody-secreting hybridoma and confirming antigen binding.

The board's analysis rested on the factual basis that the first 4 of the 10 attempts to create hybridoma fusions were failures, and that only 4 of the 143 actual fusions were tested and proven to fall within the claim scope. The board concludes from these facts a low rate of success and that the methods were not predictable or reproducible.

The Federal Circuit criticized the Board's focus on the 4 failed fusions, especially in light of Applicant's explanation that it was the result of incomplete mastery of the fusion process and

that the following 6 attempts were successful. It found absurd to use the high number of untested hybridomas as evidence of unpredictability or unreliability - in that it would lead to a logical conclusion that the more untested data an applicant generates, the less predictable their results become.

Applied in the present context, Applicants have described the preparation of variants within the claim scope. Through the transgenic animal model, they have disclosed how the function of such variants can be tested. Specifically relating to the *Wands* factors in the present context, the preparation of transgenic animal is not difficult, directions for the exact preparation in the present context if provided in the Example 11, the nature of the invention is a polypeptide and functional variants thereof, a claim type and scope that is limited, reasonable and now almost routine in the domain of patent law, the state of the prior art and the relative skill of those in the art is well advanced and the predictability of polypeptide creation and expression, as well as the preparation of transgenic animals is very well characterized and known.

Applicants respectfully request consideration and withdrawal of Claims 1-7, 11-14 and 16-18 under 35 U.S.C. § 112, First Paragraph.

The Third Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 11-14 and 16-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled that the inventors had possession of the invention.

The Examiner acknowledges that the specification provides written description for SEQ ID NO:1 and SEQ ID NO:4, but not variants thereof.

The Examiner cites *Vas-Cath v. Mahurkar,* 19 U.S.P.Q.2d 1111 for the proposition that a specification must "clearly allow persons of ordinary skill in the art to recognize what is claimed." Next, the Examiner cites *Fiers v. Revel*, 25 U.S.P.Q2d 1601, 1606 (Fed Cir. 1993) and *Amgen v. Chugai*, 18 U.S.P.Q.2d 1016 for the proposition that written description "requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it." Finally, the Examiner cites *Fiddes v. Baird*, 30 U.S.P.Q2d 1481, 1483 for tenet that one cannot describe what one has not conceived.

In response, the written description requirement prescribes that the specification must convey with reasonable clarity to those skilled in the art, that Applicants were in possession of the invention as of the filing date. *Vas-Cath v. Mahurkar*, 19 U.S.P.Q.2d. 1111, 1116 (Fed. Cir. 1991). The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient. *In re Wertheim*, 191 U.S.P.Q. 90, 98 (C.C.P.A. 1976). The determination is *factual* and depends on the nature of the invention and amount of knowledge imparted to those skilled in the art by the disclosure. *Vas-Cath* at 1116 (emphasis in original).

In *Vas-Cath*, the Federal Circuit reversed the district court's holding that a utility application failed the written description requirement over the disclosure of a prior filed design application. The claimed subject matter was a catheter comprising joined semi-circular tubes (lumens) coming to a single tapered tip, while the prior art comprised two concentric coaxial tubes. At issue was whether the drawing of the design application sufficiently described the invention for the later-filed utility applications.

The district court's analysis centered on the finding that the drawing failed to show what the invention was, be it a subset or superset of the features depicted in the drawings. "To show one example of an invention, even a working model, is not to describe what is novel or important." *Vas-Cath* at 1118.

The Federal Circuit faulted the district court's analysis, and noted that an invention is defined by the claims on appeal, not by the disclosure of the priority document. Rather than describing the particular limitations of the components of the catheter (*e.g.*, semi-circular lumens, ratio of tip tapering, shape, size and placement of inlets and outlets, *etc.*), the drawing showed a *combination* of those features, and did in fact describe the claimed invention. *Vas-Cath* at 1118.

In *Wertheim*, the Court of Customs and Patent Appeals reversed in part the Board of Interferences and Patent Appeals' ("Board") finding that the appealed claims were not entitled to priority of a prior application for lack of written description. The claimed subject matter was directed to a process for making freeze-dried instant coffee. At issue was whether the specific claim limitation describing a solids content of "at least 35%" and "between 35% and 60%" was

supported by a prior filing containing the text "between 35% and 60%" in combination with specific examples of 36% and 60%.

The Federal Circuit criticized the Boards' decision on the grounds that the PTO submitted no evidence to doubt that the claimed broader range did not also describe the narrower claimed range. Moreover, the court noted that there was no evidence of any distinction in operability or result between the claimed lower range and the disclosure. Because the PTO did not meet its initial burden to show why the description not in *ipsis verbis* was insufficient, the rejection was improper. *Wertheim* at 98.

The Examiner's reliance on *Vas-Cath* in support of the rejection for a lack of written description is misplaced. In fact, these cases support Applicants' position that the specification does in fact teach an adequate written description.

While the Examiner has already acknowledged that written description exists for SEQ ID NO:4 and the polypeptide encoded by the cDNA deposited under ATCC Dep. No. PTA-3376, the Examiners attention is focused on the description of variants having 80% sequence identity defined at page 12, line 24 through page 13, line 9. The particular methodology used to determine sequence identity if provided page 13, line 10 through page 14, line 4.

Both *Vas-Cath* and *Wertheim* dealt with an issue of whether or not a specification not in *ipsis verbis* met the requirements of written description. As described above, Applicants specification has literal or *ipsis verbis* support for the rejected subject matter, which are even more favorable facts than those of *Vas-Cath* and *Wertheim* wherein the court found a written description present.

Turning now to the issue that written description requires possession of the nucleic acid, Applicants will briefly discuss *Fiers v. Sugano*, *Amgen v. Chugai*, and *Fiddes v. Baird*.

In *Fiers*, the Federal Circuit affirmed an award of priority of invention in a 3-way interference appealed from the Board of Patent Appeals and Interferences ("Board"). At issue was the invention date of DNA encoding β-interferon. The court held that "an adequate written description of DNA requires . . . a description of the DNA itself." Applicant Sugano was therefor entitled to the invention because his priority patent application was the only one that contained the complete and correct sequence that encoded β-interferon. The other contenders for

priority either only described a method for obtaining the DNA (Fiers) or simply did not disclose the nucleotide sequence or an "intact, complete gene" (Revel). *Fiers* at 1605.

In *Amgen*, the Federal Circuit affirmed the magistrate's district court decision of no prior invention under 35 U.S.C. § 102(g). The claimed subject matter was directed to a purified and isolated DNA sequence encoding human erythropoietin (EPO). The court noted the absence of any description of physical or chemical properties so as clearly distinguish the claimed subject matter, and further instructed that a description of only biological properties alone was insufficient.

> [W]e hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it form other materials, as well as a method of obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

Amgen at 1021.

Amgen discussed the issue of possession of the invention in the context of the broader issue of conception. The Examiner appears to be relying upon *Amgen* in support of the above rejection because written description is essentially an issue of possession, or whether or not Applicants have clearly distinguished the invention from the prior art and have thereby demonstrated possession of the invention.

In *Fiddes*, the Board of Patent Appeals and Interferences denied a request for invention priority in a 2-way interference asserted in order to antedate anticipating prior art. The subject matter of the count was directed the DNA sequences encoding mammalian basic fibroblast growth factor. At issue was whether a disclosure teaching bovine pituitary FGF and a theoretical DNA sequence, without the naturally occurring gene, showed possession of all mammalian bFGF's.

The Board noted that possession of an amino acid sequence coupled with the known relationship between a nucleic acid and the protein it encodes does not establish possession of the gene encoding the protein.

In response, the Examiner's reliance upon *Fiers*, *Amgen* and *Fiddes* is misplaced. Inapposite to the common facts of *Fiers*, *Amgen* and *Fiddes*, Applicants do in fact describe the

nucleic acid encoding SEQ ID NO:1 in Figure 1A. As the priority winner in *Fiers*, Applicants teach the disclosure of nucleic acid. Unlike *Amgen*, which used only a functional limitation to define the claim scope, Applicants have both structural (% sequence identity) and functional (transgenic animal phenotype) limitations defining the present claims scope. Unlike *Fiddes*, Applicants teach both the complete and correct DNA sequence encoding SEQ ID NO:1, rather than a hypothetical sequence. Moreover, rather than a vague limitation to mammalian gene homologs, the present claims contain both a narrowly focused structural limitation of 80% sequence identity to SEQ ID NO:1 coupled with the functional limitation of inducing (1) lower relative weight, (2) lower fat/total body weight ratio, and (3) greater lean muscle mass/total body weight ration. One of ordinary skill can readily apply the present claim limitations to clearly describe the claimed subject matter and readily distinguishes it from the prior art.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-7, 11-14 and 16-18 under 35 U.S.C. § 112, First Paragraph.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding objections and rejections be withdrawn and this case passed to issue. No new matter has been introduced, and entry of these amendments is respectfully requested. Reconsideration and further examination of the claims is respectfully requested.

The examiner is invited to contact the undersigned at (650) 225-1489 in order to expedite the resolution of any remaining issues.

Respectfully submitted,
GENENTECH, INC.

Date: June 16, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph at page 17, lines 12-19 has been amended as follows:

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 ~~m~~μg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

In the claims:

Claims 1-13 and 15 have been amended as follows:

1 (Amended). An isolated nucleic acid molecule which comprises DNA encoding a polypeptide having at least about 80% sequence identity to: (a) ~~a DNA molecule encoding~~ an NS4 polypeptide ~~comprising~~having the sequence of amino acid residues from about ~~(i)~~ 1 or about 20 to about 87, inclusive, of Figure 2A (SEQ ID NO:4), ~~(ii) 1 or about 20 to about 95, inclusive, of Figure 2B (SEQ ID NO:5) or (iii) 1 or about 20 or about 95, inclusive, of Figure 2C (SEQ ID NO:6);~~ or (b) the complement of the DNA molecule of (a).

2 (Amended). The isolated nucleic acid molecule of Claim 1 comprising the sequence of nucleotide positions from about: ~~(i)~~ 486 or about 543 to about 746, inclusive, of Figure 1A (SEQ ID NO:1)~~; (ii) 1784 or about 1841 to about 2068, inclusive, of Figure 1B (SEQ ID NO:2) or (iii) 447 or about 504 to about 731, inclusive, of Figure 1C (SEQ ID NO:3)~~.

3 (Amended). The isolated nucleic acid molecule of Claim 1 comprising a nucleotide sequence that encodes the sequence of amino acid residues from about (i) 1 or about 20 to about 87, inclusive, of Figure 2A (SEQ ID NO:4)~~; (ii) 1 or about 20 to about 95, inclusive, of Figure 2B (SEQ ID NO:5) or (iii) 1 or about 20 or about 95, inclusive, of Figure 2C (SEQ ID NO:6)~~.

4 (Amended). An isolated nucleic acid molecule comprising DNA encoding a polypeptide having ~~which comprises~~ at least about 80% sequence identity to (a) ~~a DNA molecule encoding~~ the same mature polypeptide encoded by the human cDNA deposited with the ATCC on ~~(i)~~ May 15, 2001 under ATCC Deposit No. PTA-3376 (DNA146649-1789R1)~~, (ii) April 4, 2000 under ATCC Deposit No. PTA-1627 or (iii) May 31, 2000 under ATCC Deposit No. PTA-1971 (DNA149995-2871)~~, or (b) the complement of the DNA molecule of (a).

5 (Amended). The isolated nucleic acid molecule of Claim 4 comprising (a) DNA encoding the same mature polypeptide encoded by the human cDNA deposited with the ATCC on ~~(i)~~ May 15, 2001 under ATCC Deposit No. PTA-3376 (DNA146649-1789R1), ~~(ii) April 4, 2000 under ATCC Deposit No. PTA-1627 or (iii) May 31, 2000 under ATCC Deposit No. PTA-1971 (DNA149995-2871),~~ or (b) the complement of the DNA molecule of (a).

6 (Amended). An isolated nucleic acid molecule comprising DNA having at least about 80% nucleic acid sequence identity to the ~~full-length polypeptide~~ coding sequence of the human cDNA deposited with the ATTC on: (a) ~~(i)~~ May 15, 2001 under ATCC Deposit No. PTA-3376 (DNA146649-1789R1), ~~(ii) April 4, 2000 under ATCC Deposit No. PTA-1627 or (iii) May 31, 2000 under ATCC Deposit No. PTA-1971 (DNA149995-2871);~~ or (b) the complement of the DNA molecule of (a).

7 (Amended). The isolated nucleic acid molecule of Claim 6 comprising the ~~full-length polypeptide~~ coding sequence of the human protein cDNA deposited with the ATCC on: (a) ~~(i)~~ May 15, 2001 under ATCC Deposit No. PTA-3376 (DNA146649-1789R1), ~~(ii) April 4, 2000 under ATCC Deposit No. PTA-1627 or (iii) May 31, 2000 under ATCC Deposit No. PTA-1971 (DNA149995-2871);~~ or (b) the complement of the DNA molecule of (a).

8 (Amended). An isolated nucleic acid molecule encoding a NS4 polypeptide comprising DNA that hybridizes under at least moderately stringent conditions to the complement of the nucleic acid sequence that encodes amino acids ~~(i)~~ 1 or about 20 to about 87, inclusive, of Figure 2A (SEQ ID NO:4), wherein the hybridization occurs in the presence of 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37°C-50°C; ~~(ii) 1 or about 20 to about 95, inclusive, of Figure 2B (SEQ ID NO:5) or (iii) 1 or about 20 or about 95, inclusive, of Figure 2C (SEQ ID NO:6)~~.

9 (Amended). The isolated nucleic acid molecule of Claim 8, wherein the nucleic acid ~~that encodes amino acids acids: (i) 1 or about 20 to about 87, inclusive, of Figure 2A (SEQ ID NO:4); (ii) 1 or about 20 to about 95, inclusive, of Figure 2B (SEQ ID NO:5) or (iii) 1 or about 20 or about 95, inclusive, of Figure 2C (SEQ ID NO:6) comprising~~ comprises a sequence of nucleotides complementary to ~~(i)~~ 486 or about 543 to about 746, inclusive, of Figure 1A (SEQ ID NO:1)~~, (ii) 1784 or about 1841 to about 2068, inclusive, of Figure 1B (SEQ ID NO:2) or (iii) 447 or about 504 to about 731, inclusive, of Figure 1C (SEQ ID NO:3), respectively~~.

10 (Amended). The isolated nucleic acid molecule of Claim 9, wherein the hybridization occurs under stringent hybridization and wash conditions, wherein the hybridization occurs in the presence of 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

11 (Amended). An isolated nucleic acid molecule comprising at least 31 nucleotides and which is produced by hybridizing a test DNA molecule under stringent hybridization conditions with (a) a DNA molecule which encodes a NS4 polypeptide comprising a sequence of amino acid residues from about ~~(i)~~ 1 or about 20 to about 87, inclusive, of Figure 2A (SEQ ID NO:4)~~; (ii) 1 or about 20 to about 95, inclusive, of Figure 2B (SEQ ID NO:5) or (iii) 1 or about 20 or about 95, inclusive, of Figure 2C (SEQ ID NO:6)~~, or (b) the complement of the DNA molecule of (a), and isolating the test DNA molecule.

12 (Amended). The isolated nucleic acid molecule of Claim ~~12~~11, which has at least about 80% sequence identity to (a) or (b).

13 (Amended). A vector comprising the nucleic acid molecule of subclaim (a) of Claim 1.

14. The vector of Claim 13, wherein said nucleic acid molecule is operably linked to control sequences recognized by a host cell transformed with the vector.

15 (Amended). A nucleic acid molecule deposited with the ATCC under accession number ~~(i)~~ PTA-3376 (DNA146649-1789R1)~~, (ii) PTA-1627 or (iii) PTA-1971 (DNA149995-2871)~~.

16. A host cell comprising the vector of Claim 13.

17. The host cell of Claim 16, wherein said cell is selected from the group consisting of a CHO, *E. coli* and yeast.

18. A process for producing a NS4 polypeptide comprising culturing the host cell of Claim 17 under conditions suitable for expression of said NS4 polypeptide and recovering said NS4 polypeptide from the cell culture.